Pergamon

Tetrahedron 57 (2001) 1699–1708

TETRAHEDRON

Improved synthesis of functionalized molecular platforms related to marine cyclopeptides

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Received 1 September 2000; accepted 21 December 2000

Abstract—We report an improved synthesis of new molecular platforms, functionalized for studies in molecular recognition and combinatorial chemistry. Their structures are related to naturally occurring marine cyclopeptides such as the Dolostatins and Dendroamides that feature side chain functionality positioned on the same face of a rigid platform. Incorporation of methyl substituted oxazole and thiazole rings into the platforms enhances the rigidity of structure and significantly improves the yields of the macrocyclization reaction in the synthesis.

1. Introduction

In recent years there has been rapid progress in the field of isolation and characterization of natural marine cyclopeptides,[1] especially those incorporating five-membered heterocyclic rings.[2] These compounds are usually metabolic products of primitive marine organisms, algae, fungi and often possess significant biological activities, including cytotoxicity, antibacterial and antiviral activities.[3] Examples have also been found for their ability to overcome multidrug resistance or to act as antineoplastic agents.[4]

Dendroamide C (**1**),[4a] Bistatramide D (**2**),[2b] Westiellamide (**3**)[5] (Fig. 1) and numerous other natural cyclopeptides can be identified as biologically modified hexapaptide derivatives.[3a,6] These modifications include not only macrocyclization, but also heterocyclization of serine, threonine and cysteine side chains onto the backbone carbonyl groups to create five-membered heterocyclic rings (e.g. oxazoles, thiazoles and oxazolines).[3a] In cases where three aromatic heterocycles are linked together with *trans*-amide bonds in a macrocycle the structure becomes rigid and nearly planar. This rigidity is further stabilized by the intramolecular array of hydrogen bond donors and acceptors—the hydrogens of the secondary amides and the lone pairs of the heterocyclic nitrogens—all directed to the center of the macrocycle. There does not appear to be enough space in the center to accommodate even a single water molecule, and solvation of the amides must occur at the peripheral oxygens rather than the inwardly directed hydrogens. This feature may contribute to the transport properties of these compounds across biological membranes.

The orientation of the side-chain substituents, of course, depends on the configuration at the α carbon atoms. All-*syn* substituted analogues, especially with functionalized side-chains [e.g. Dendroamide A, B, C (**1**)[4a] and Dolastatine 3[4b]] are rare among the marine cyclopeptides characterized to date. Accordingly, synthesis provides the best access to these structures which might also play roles as core molecules for solution phase combinatorial chemistry and as templates for synthetic receptors.[7] In the former role, the macrocycle offers sizeable dimensions and three addresses. These large surface areas are likely to be required for interfering with protein–protein and protein–nucleic acid interactions. In the latter role, the macrocycle's rigidity suggests its use as a spacer element on which functional groups may be presented, preorganized for selective molecular recognition of smaller molecular targets. These roles are by no means unrelated, but require the efficient synthetic procedures that we relate here.

Platform **4** (Fig. 2)—synthesized earlier[8]—was a promising candidate for these purposes, but the macrocyclization step ending the stepwise synthesis proved a limiting factor due to the low yields (13–15%). This was puzzling because the same attributes that contribute to the rigidity of the final

Keywords: platforms; macrocyclization; oxazoles and thiazoles; combinatorial chemistry.

Abbreviations: Boc: *t*-butyloxy-carbonyl; ^{t}Bu: *t*-butyl; Bzl: benzyl; DAST: (diethylamino)sulfur trifluoride; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM: dichloromethane; DIEA (*Hünig's base*): *N*,*N*-diisopropylethylamine; DMAP: 4-dimethylaminopyridine; DMF: *N*,*N*-dimethylformamide; DPPA: diphenylphosphoryl azide; EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; FDPP: pentafluorophenyl diphenylphosphinate; HBTU: 2-(1H-benztriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt: 1-hydroxybenztriazole; PyBOP: benztriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; TBAF: tetrabutylammonium fluoride hydrate; TBC: 2,4,6-trichlorobenzoyl chloride; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TMSI: iodotrimethylsilane; Z: benzyloxycarbonyl.

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PII: S0040-4020(00)01173-X

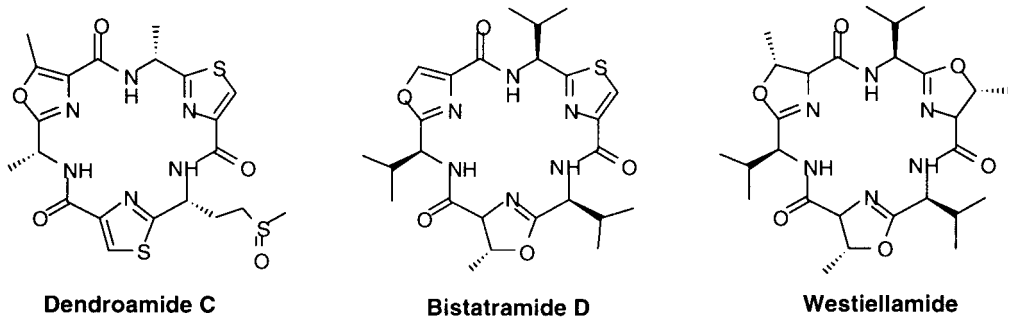


Figure 1. Natural marine cyclopeptide platforms with all-*syn* side chains.

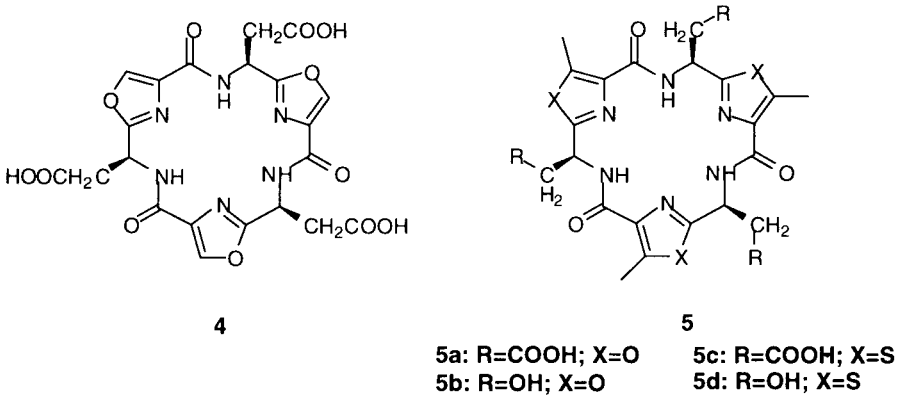


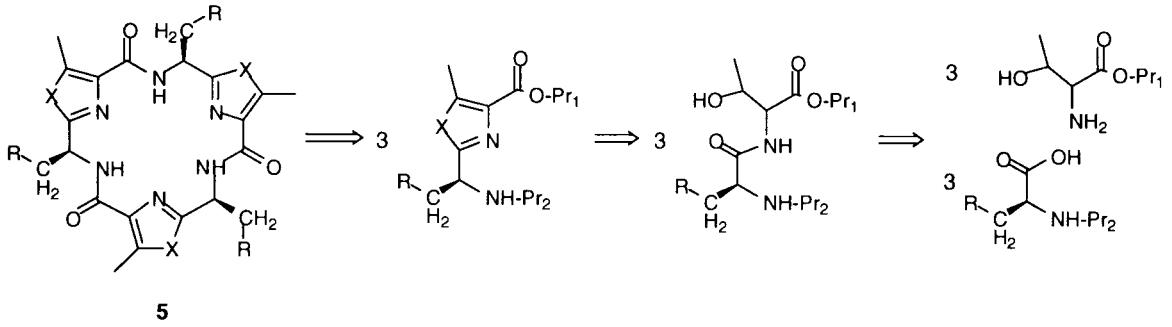
Figure 2. Side chain functionalized synthetic analogues with C_3 symmetry.

structure should stabilize the transition state conformation for the macrocyclization. One solution to the problem was discovered by Wipf and coworkers,[2f] who fashioned the five-membered heterocycles *after* the macrocyclization step. Their improved yields suggested that the simple oxazole or thiazole derivatives somehow resist macrocyclization with respect to other processes. It seemed possible that the fraction of the intermolecular coupling products could be reduced by altering these heterocycles, by limiting access of nucleophiles to the activated carboxyl of the macrocyclic precursor. Accordingly, we synthesized new core molecules with C_3 symmetry (see general structure **5** in Fig. 2) featuring methyl substituted oxazole and thiazole units in the macrocyclic ring. This did enhance the cyclization step and yields up to 69% were obtained. In addition, a stepwise synthetic route to orthogonally protected cyclotrimers was developed in a way that the side-chain functions can be addressed selectively.

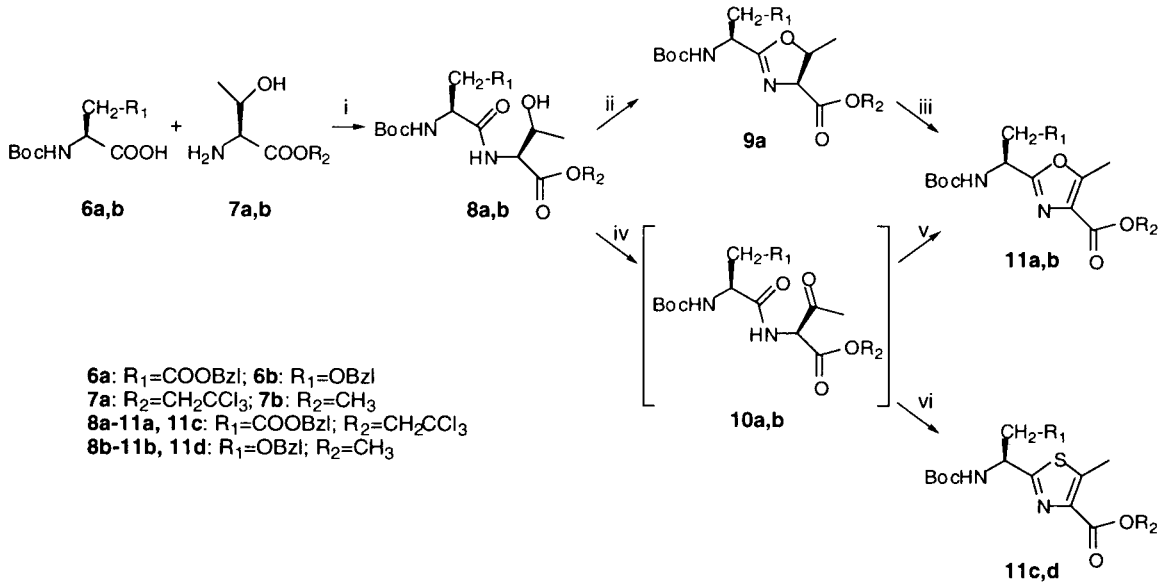
2. Results and discussion

The synthetic approach hardly merits the term 'retrosynthetic disconnection' but Scheme 1 outlines the heterocyclic modules and the suitably protected acylamino threonine derivatives that lead ultimately to **5**. Many other isosteric heterocyles such as oxadiazoles can be considered and have recently been made from appropriate acylamino oxalic acid derivatives.[9] Starting from two amino acid components (**6a**,**b** and **7a**,**b** see Scheme 2) we coupled them to form dipeptides (**8a** or **b**) through conventional peptide procedures. (For the synthesis of compound **7a** see Section 4. The other amino acid residues are commercially available.) The yields for the amide bond formation reactions were anticipated and found to be quite high (90–95%).

The heterocyclic ring was fashioned in two different ways. The first involved the cyclodehydration of dipeptide **8a** to



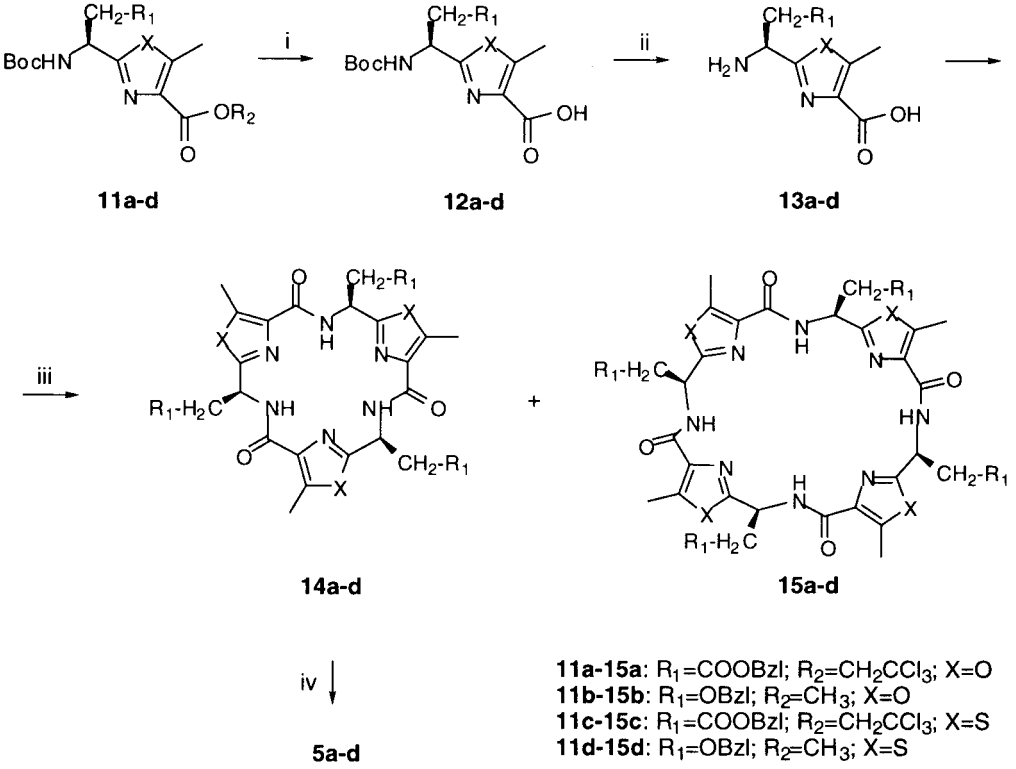
Scheme 1. Retrosynthetic disconnection of general platform **5**.



Scheme 2. Synthesis of modules: (i) HBTU, HOBt, Et_3N, DMF, −20°C to rt, 20 h, 92% for **6a** and **7a**; DPPA, DIEA, DMF, 0°C to rt, 20 h, 95% for **6b** and **7b**; (ii) DAST, CH_2Cl_2, −78°C, 2 h; (iii) $BrCCl_3$, DBU, CH_2Cl_2, 0°C to rt, 20 h, 23% for (ii) and (iii); (iv) Dess–Martin periodinane, CH_2Cl_2, 0°C to rt, 4–6 h; (v) PPh_3, I_2, Et_3N, CH_2Cl_2, 0°C to rt, 1 h, 46–65% for (iv) and (v); (vi) Lawesson's reagent, THF, reflux, 5 h, 54–65% for (iv) and (vi).

the appropriate oxazoline derivative **9a** by (diethylamino) sulfur trifluoride (DAST)[10] at −78°C in 2 h. This was followed by oxidation with $BrCCl_3$ in the presence of DBU[11] to afford subunit **11a** in 23% yield.

Alternatively—and more successfully—the dipeptides were subjected to oxidation using the Dess–Martin periodinane[12] to form amidoketone derivatives **10a** or **b**. These were transformed without purification into either the oxazole or the thiazole modules (**11a–d**) using PPh_3 in the presence of I_2 and Et_3N[13] or Lawesson's reagent,[14] respectively. The yields for the protected modules, calculated from the dipeptides, were considerably higher (46–65%) by this route.



Scheme 3. One-pot cyclization of modules: (i) Zn, 90% aqueous AcOH, rt, 5 h, quant., for **11a** and **c**; 2 M aqueous NaOH, MeOH/dioxane, 0°C to rt, 20 h, quant., for **11b** and **d**; (ii) TFA, CH_2Cl_2, 1/2–3 h, quant.; (iii): see Table 1; (iv): H_2, 10%Pd–C, EtOAc, 20 h, quant. for **14a**; H_2, Pearlman's catalyst, EtOH/EtOAc, 2 days, 90% for **14b**; $(CH_3)_3SiI$, $CHCl_3$, 40°C, 12 h, for **14c** and **d**.

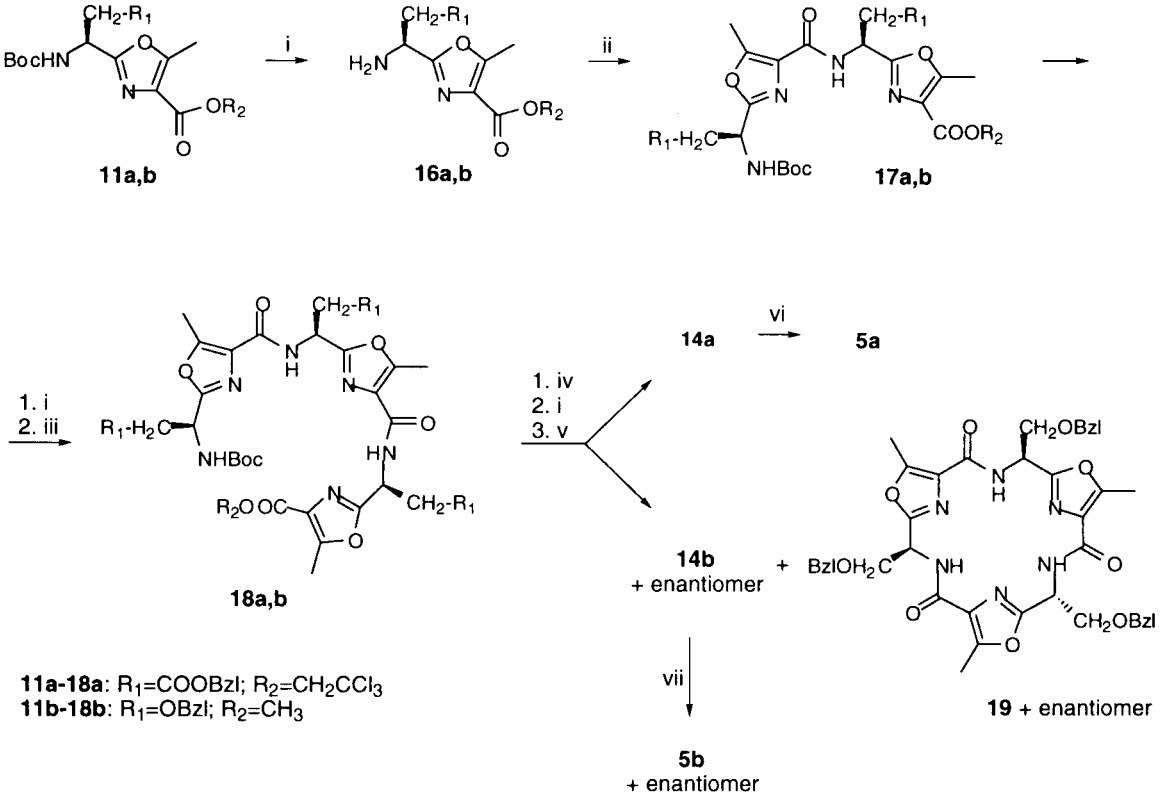
Table 1. Reaction conditions for the one-pot cyclization of amino acid modules

Monomer	Coupling reagent	Concentration (mol/l)	Solvent	Reaction time (days)	Yield (%)	
					Trimer (**14a–d**)	Tetramer (**15a–d**)
13a	DPPA	0.01	DMF	7	18	n/i
	FDPP	0.05	ACN	7	25	n/i
	PyBOP	0.05	DMF	7	24	n/i
	PyBOP	0.05	DMF	14	38	24
13b	DPPA	0.02	DMF	4	35	n/i
13c	PyBOP	0.05	DMF	14	36	16
13d	DPPA	0.02	DMF	5	22[a]	n/i

In a general cyclization procedure 2 equiv. of coupling reagent was added to 1 equiv. of monomer in the presence of 10 equiv. of DIEA; n/i: not isolated.
[a] 7% of *syn–syn–anti* diastereomer was also isolated.

Two methods for the macrocyclization of the monomeric modules (**11a–d**) were examined: a 'one-pot' procedure and the stepwise route. In Scheme 3 and in Table 1 we summarize our results from one-pot reactions. These involved deprotection of the carboxyl and the amino terminus of monomeric compounds **11a–d** and afforded the TFA salts of the appropriate amino acid modules **13a–d**. These underwent cyclooligomerization upon treatment with common peptide coupling reagents (PyBOP, FDPP, DPPA) in the presence of Hünig's base over a time span of 4–14 days. These findings are in agreement with the data from other laboratories for similar, non-functionalized oxazoline[5] and thiazole[15] compounds.

Nevertheless, there were some differences worth pointing out. First, the yields of the enantiomerically pure, functionalized cyclotrimers (**14a–d**) are usually high enough (35–38%) to afford these macrocycles on a gram scale. Second, the cyclotrimers can easily be separated by column chromatography on silica gel from cyclotetramers (**15a** and **c**) or from any other by-products, including diastereomeric cyclotrimers (see Table 1). The formation of the *syn–syn–anti* diastereomer beside the usually isolated all-*syn* compound (**14d**) is most likely the result of partial epimerization at the chiral center during the methyl ester deprotection of building block **11d** under basic conditions (see Scheme 3). Bzl protecting groups were removed under

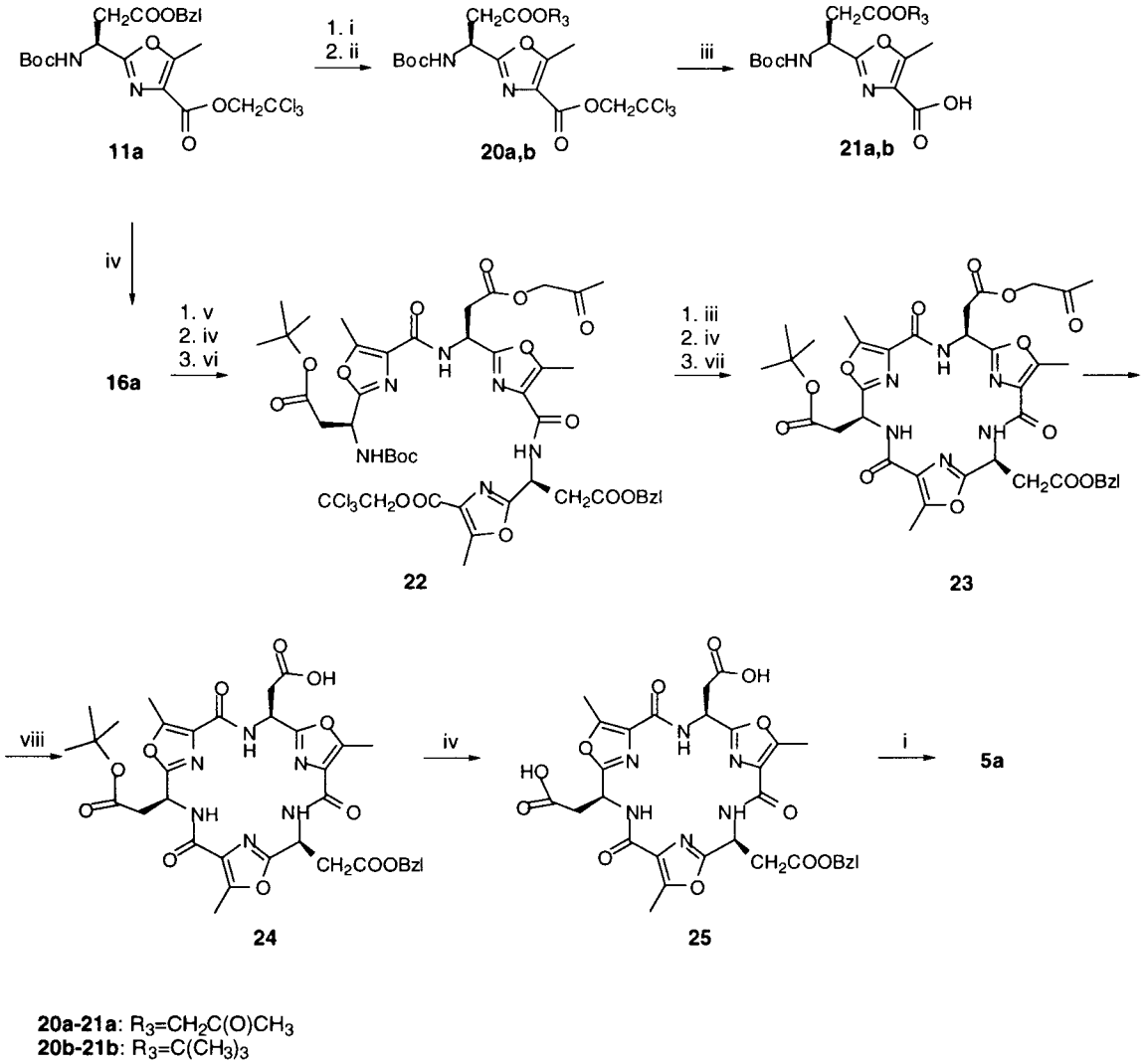


Scheme 4. Stepwise procedure for the cyclization of modules: (i) TFA, CH_2Cl_2, 1/2–3 h, quant.; (ii) HBTU, HOBt, Et_3N, **12a**, DMF, −20°C to rt, 20 h, 64% for **16a**; PyBOP, DIEA, **12b**, DMF, rt, 24 h, 72% for **16b**; (iii) HBTU, HOBt, DIEA, **12a**, DMF, −20°C to rt, 20 h, 64% for **17a**; PyBOP, DIEA, **12b**, DMF, rt, 40 h, 89% for **17b**; (iv) Zn, 90% aqueous AcOH, rt, 5 h, quant., for **18a**; 2 M aqueous NaOH, MeOH/dioxane, 0°C to rt, 20 h, quant., for **18b**; (v) PyBOP, DIEA, rt, 4 days, 69% of **14a** for **18a**; same conditions but 15% of **14b**+enantiomer and 26% of **19**+enantiomer for **18b**; (vi) H_2, 10%Pd–C, EtOAc, 20 h; (vii) H_2, Pearlman's catalyst, EtOH/EtOAc, 2 days.

catalytic hydrogenolysis to afford oxazole containing platforms **5a** and **5b**, and using TMSI for platforms **5c** and **5d** incorporating thiazole rings.

Third, substantial amounts of cyclotetramers were recovered from the reaction mixtures only if longer reaction times were used. (Table 1) The formation of cyclic products most likely follows a stepwise fashion through linear dimers and trimers; tetramers can arise by both 3+1 and 2+2 condensations. Cyclotetramers incorporating five-membered heterocycles into the macrocycle are also well known among natural cyclopeptides.[16] The interactions between the lone pairs of the oxazole or thiazole nitrogens and the hydrogens of the secondary amides—their 'intramolecular hydrogen bonds'—are probably weaker than those of cyclotrimers. The ^{1}H NMR spectra show the doublets of the amide NH resonances shifted about 0.5 ppm upfield of those of the cyclotrimers. The structures of cyclotetramers also appear to be more flexible, so these molecules are less desirable targets to serve as e.g. templates for synthetic receptors. Doubtless larger cyclooligomers are formed during the one-pot reactions,[17] but we have not attempted their isolation.

The fourth observation concerns the salubrious effect of the additional methyl substituent on the oxazole or thiazole heterocycles. A similar example from the literature is the one-pot synthesis of the natural trioxazoline derivative Westiellamide (**3**)[5]. The authors were able to isolate not only the cyclotrimer, but also the cyclotetramer in fairly high yields, 20 and 25%, respectively. The extra methyl group attached to the oxazoline ring may have contributed to these yields. We tested the effect of the methyl group on cyclization through a module made from a serine derivative instead of threonine. The protective groups were the same as of **11a**. After the deprotection of the carboxyl and the amino functions (see Scheme 3) the cyclooligomerization was performed using PyBOP in the presence of Hünig's base in DMF (0.05 M) for 14 days. The Bzl-esters of both the appropriate cyclic trimer **4** and cyclic tetramer were each



Scheme 5. Synthesis of orthogonally protected platform: (i) H_2, 10% Pd–C, EtOAc, 20 h; (ii) TBC, Et_3N, THF, $CH_3C(O)CH_2OH$, DMAP, CH_2Cl_2, 83% for **20a**; TBC, Et_3N, THF, ^{t}Bu–OH, DMAP, CH_2Cl_2, 52% for **20b**; (iii) Zn, 90% aqueous AcOH, rt, 5 h, quant., (iv) TFA, CH_2Cl_2, 1/2–3 h, quant.; (v) HBTU, HOBt, DIEA, **21a**, DMF, −20°C to rt, 4days, 68%; (vi) HBTU, HOBt, DIEA, **21b**, DMF, −20°C to rt, 4 days, 32%; (vii) PyBOP, DIEA, rt, 10 days, 24% calculated from linear trimer **22**; (viii) TBAF, THF, rt, 80%.

isolated in 12% yield. These yields are substantially lower than those from **13a** (38% for cyclic trimer **14a** and 24% for cyclic tetramer **15a**). The cyclization-inducing effect of the 'extra' methyl substituent is apparent.

Further to this point, we also synthesized triacid platform **5a** and trialcohol platform **5b** by the longer stepwise route. (Scheme 4) The oxazole modules **11a** and **11b** were deprotected separately on the carboxyl and the amino terminus to give free acid monomers **12a** and **12b** and TFA salts of **16a** and **16b**, respectively. These monomers were coupled to form protected dimers **17a** and **17b** again using conventional peptide coupling procedures. Boc cleavage and coupling with acid modules (**12a** and **b**) were repeated to afford enantiomerically pure linear trimers **18a** and **18b**. Protecting groups were removed from the carboxyl and amino termini and the linear trimer modules were subjected to cyclization with PyBOP and Hünig's base in DMF.[18] The reactions were worked up after 4 days and the crude mixtures were purified on silica gel. The enantiomerically pure tri-benzyl ester platform **14a** was isolated in 69% yield from **18a**. From **18b** we found 26% of the diastereomeric compounds (**19** and its enantiomer) beside 15% of the symmetric macrocycles (**14b** and its enantiomer). The probable cause of diastereomerization again is the epimerization at the chiral centers during methyl ester deprotection under basic conditions. This epimerization could be eliminated by only using protective groups removable under neutral or acidic conditions (see module **11a**) or by replacing the hydrogen at the chiral center with a methyl group.[19]

There is a striking difference between the yields of cyclization for the oxazole platform **5a** (69%) and platform **4** (13–15%)[8] lacking the extra methyl groups. Whether this effect involves preorganization to a sickle shape appropriate for cyclization or prevention of higher oligomers through steric hindrance of external nucleophiles is unknown.

Addressable side chains are available through the methods outlined in Scheme 5. From module **11a** the orthogonally protected triester platform **23** was assembled. First, modules **20a** and **20b** were prepared by removing the Bzl ester group under catalytic hydrogenolysis and re-protecting the free side-chain carboxyl with acetol[20] and *tert*-butyl groups, respectively, using Yamaguchi's procedure.[21] These new modules were transformed to the free acid derivatives (**21a** and **21b**) then coupled to the amino building block **16a.** The protected linear trimer compound **22** (Scheme 5) was obtained through coupling procedures described previously (Scheme 4). Deprotection of the trichloroethyl ester afforded the free acid derivative as usual, but cleavage of the Boc group under acidic conditions caused the ^{t}Bu-ester to be partly deprotected as well. (According to the integration of the ^{1}H NMR amide NH signals the ratio between the desired compound and the over-deprotected one was 2:1.) Cyclization in DMF with PyBOP activation in the presence of DIEA for 10 days yielded the orthogonally protected triester platform **23** in 24% from protected linear trimer **22**. The carboxyl-protecting groups were removed step-by-step using TBAF, TFA and catalytic hydrogenolysis to give mono- (**24**), di- (**25**) and triacid (**5a**) platforms, respectively.

3. Conclusions

The synthetic molecular platforms described above have features that can make them ideal candidates for studies in molecular recognition and combinatorial chemistry. Besides the fairly rigid, almost planar heterocyclic ring-system—found also in natural analogues—they possess functionalized side-chains on the same face of the molecule. Investigations revealing their behavior as core molecules are currently underway in our laboratories. Our experiments have shown that both the one-pot and the stepwise synthetic routes can afford these functionalized molecular platforms on a gram scale. The incorporation of methyl substituted heterocycles into the macrocyclic ring was proven to enhance the yield of the macrocyclization step. The additional methyl group presumably helps to preorganize the structure of the linear oligomer compound into a sickle shape better suited for cyclization. The selectively addressable, side-chain functionality opens the way to diversification through combinatorial synthesis.

4. Experimental

4.1. Spectroscopy, purifications and abbreviations

All reactions were performed under N_2 atmosphere and NMR spectra were recorded on a Bruker DRX 600 spectrometer; the chemical shifts are given in ppm relative to TMS. The spectra were referenced to deuterated solvents indicated in brackets in the analytical data. High resolution MALDI-FTMS measurements were performed on an IonSpec FTMS mass spectrometer using 2,5-dihydroxybenzoic acid matrix. The electrospray ionization (ESI) mass spectrometry experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer. TLC: silica gel plates IB2-F; J. T. Baker Column chromatography: silica gel 60; 230–400 mesh; E. Merck KGaA. Preparative chromatographic plates: silica gel 60 F_{254} (20×20 cm^2, 0.5 mm). Anhydrous solvents and chemicals were used as purchased from commercial suppliers.

4.2. General procedures

(1) *Cleavage of the trichloroethyl-ester group*. To a stirred solution of protected compound (1 equiv.) in glacial acetic acid/water=9:1 (0.01 M) Zn powder (20–50 equiv.) was added slowly at rt. The mixture was stirred until TLC showed the consumption of all starting material (usually 5 h), then filtered and concentrated in vacuo. The residue was taken into EtOAc, extracted with 5% HCl solution, water and brine, then dried over $MgSO_4$ and concentrated to give the pure acid residue. (2) *Cleavage of the methyl-ester group*. Protected compound (0.05 M) was dissolved in a mixture of methanol/dioxane=10:7 followed by the slow addition of 2 M NaOH solution (10 equiv.) at 0°C. Stirring was continued for 20 h and the reaction mixture was allowed to warm slowly to rt. The organic solvents were removed in vacuo followed by addition of water and 1 M HCl solution. The aqueous phase was repeatedly extracted with DCM, the organic layers were combined and dried over $MgSO_4$, then concentrated in vacuo to give the pure acid compound. (3) *Cleavage of the Boc group*. Protected

compound was dissolved in anhydrous DCM (0.1 M) and TFA (50–100 equiv.) was added slowly at rt. Stirring was continued until TLC showed the consumption of all starting material (usually 0.5–3 h). The mixture was concentrated in vacuo to yield the TFA salt of the pure deprotected amino compound. (4) *Peptide coupling conditions*. To a stirred solution of acid compound (1 equiv.) and the TFA salt of the amino compound (1.2 equiv.) in DMF (0.2 M) were added HBTU (1.2 q) and HOBt (1.2 equiv.) at −20°C, followed by the slow addition of TEA or DIEA (3.6 equiv.). Stirring was continued for 20 h while the mixture was allowed to warm to rt. Solvent was evaporated and the residue was dissolved in EtOAc, then extracted with 5% aqueous HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ or Na_2SO_4 and concentrated in vacuo. Purification was accomplished by chromatography on silica gel with an EtOAc/hexanes mixture as eluent.

4.2.1. Synthesis of the TFA salt of H-(L)-Thr-OCH_2CCl_3 (7a). To a stirred solution of Boc-(L)-Thr-OH (1 equiv.) in CH_2Cl_2 (0.3 M) were added CCl_3CH_2OH (1.5 equiv.), EDCI (1.2 equiv.) and HOBt (1.2 equiv.), followed by the slow addition of DIEA (3.6 equiv.) at −20°C. The mixture was stirred overnight and allowed it to warm up to rt. Solvent was evaporated and the residue was partitioned between EtOAc and 5% aqueous HCl solution. The organic layer was further extracted with saturated $NaHCO_3$ solution and brine, then dried over $MgSO_4$ and concentrated in vacuo to afford Boc-(L)-Thr-OCH_2CCl_3 in 90%. The Boc group was removed as described above to give the TFA salt of compound **7a**.

4.2.2. Synthesis of Boc-[(L)-Asp(OBzl)-(L)-Thr]-OCH_2CCl_3 (8a). General procedure for peptide coupling was used. Acid compound: Boc-(L)-Asp(OBzl)-OH (**6a**), amino compound: H-(L)-Thr-OCH_2CCl_3 (**7a**), purification: EtOAc/hexanes=1:2 to yield pure dipeptide **8a** as a yellow oil in 92%. ^{1}H NMR (acetone-d_6): 7.48 (d, J=8.8 Hz, 1H, NH); 7.41–7.32 (m, 5H); 6.57 (d, J=8.2 Hz, 1H, NH); 5.15 (AB, J=13.3 Hz, 1H); 5.13 (AB, J=13.3 Hz, 1H); 4.91 (AB, J=12.1 Hz, 1H); 4.85 (AB, J=12.1 Hz, 1H); 4.66 (m, 1H); 4.60 (dd, ^2J=8.8 Hz, ^3J=2.5 Hz, 1H); 4.47 (m, 1H); 4.33 (d, J=4.6 Hz, 1H, OH); 2.98 (dd, ^2J=16.5 Hz, ^3J=5.7 Hz, 1H); 2.84 (dd, ^2J=16.5 Hz, ^3J=7.4 Hz, 1H); 1.42 (s, 9H); 1.22 (d, J=6.3 Hz, 3H). ^{13}C NMR (acetone-d_6): 172.2; 171.5; 170.0; 156.5; 137.3; 129.2; 128.9; 95.9; 80.0; 75.0; 67.9; 66.9; 58.6; 52.1; 36.8; 28.6; 20.7. MALDI-FTMS $[M+Na]^+$: calculated: 577.0882; observed: 577.0886.

4.2.3. Synthesis of Boc-[(L)-Ser(Bzl)-(L)-Thr]-OCH_3 (8b). To a stirred solution of Boc-(L)-Ser(Bzl)-OH (**6b**) (1 equiv.), the HCl salt of H-(l)-Thr-OCH_3 (**7b**) (1.5 equiv.) and DIEA (1.5 equiv.) in DMF (0.3 M) was added DPPA (1.5 equiv.) at 0°C followed by slow addition of 3.8 equiv. DIEA. The work-up was as described in Section 4.2. Purification: EtOAc/hexanes=1:2. Yield of **8b** as a yellow oil: 95%. ^{1}H NMR (acetone-d_6): 7.44–7.24 (m, 6H); 6.25 (s, 1H); 4.58 (m, 2H); 4.50 (m, 1H); 4.42 (m, 1H); 4.31 (m, 1H); 4.17 (m, 1H); 3.84 (m, 1H); 3.74 (m, 1H); 3.68 (s, 3H); 1.43 (s, 9H); 1.15 (d, J=6.6 Hz, 3H). ^{13}C NMR (acetone-d_6): 171.8; 171.3; 156.4; 139.3; 129.1; 128.6; 128.4; 79.7; 73.7; 71.1; 68.3; 58.6; 55.4; 52.4; 28.6; 20.6. MALDI-FTMS $[M+Na]^+$: calculated: 433.1945; observed: 433.1961.

4.2.4. Synthesis of oxazole building block 11a. (1) To a stirred solution of dipeptide **8a** (1 equiv.) in DCM (0.05 M), DAST reagent (1.1 equiv.) was added slowly at −78°C. The mixture was stirred for 2 h and poured into saturated K_2CO_3 solution at 0°C and the aqueous phase was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give oxazoline compound **9a**. The oxazoline **9a** was dissolved in anhydrous DCM (at 0.1 M) at 0°C and DBU (~1.2 equiv.) was added followed by the slow addition of $BrCCl_3$ (~1.2 equiv.). The mixture was stirred for 20 h and slowly warmed to rt, then extracted with saturated NH_4Cl solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Pure oxazole building block **11a** was obtained in 23% after chromatography on silica gel with EtOAc/hexanes=1:4. (2) To a stirred solution of dipeptide **8a** (1 equiv.) in DCM (0.1 M) Dess–Martin periodinane (1.5 equiv.) was added at 0°C. The ice bath was removed after 30 min and the mixture was stirred for four more hours at rt. To this mixture saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ solutions were added and stirring was continued for 45 min. The phases were separated, the organic layer was washed with brine, dried over Na_2SO_4 then concentrated in vacuo to afford amidoketon **10a** which was used without further purification. To the stirred solution of **10a** (0.05 M) in DCM, triphenylphosphine (2 equiv.), iodine (2 equiv.) and TEA (4 equiv.) were added at 0°C. The cooling bath was removed after 20 min and stirring was continued at rt for 1 h. To this mixture saturated $Na_2S_2O_3$ solution was added and stirring was continued overnight. The phases were separated and the organic layer was diluted with Et_2O. After filtration of the precipitate, the filtrate was concentrated in vacuo. Pure oxazole **11a** was obtained in 46% after chromatography on silica gel with EtOAc/hexanes=1:4. ^{1}H NMR (acetone-d_6): 7.38–7.31 (m, 5H); 6.69 (d, J=8.6 Hz, 1H, NH); 5.28 (m, 1H); 5.14 (s, 2H); 5.08 (s, 2H); 3.17 (dd, ^2J=16.3 Hz, ^3J=6.8 Hz, 1H); 3.05 (dd, ^2J=16.3 Hz, ^3J=6.8 Hz, 1H); 2.64 (s, 3H); 1.42 (s, 9H). ^{13}C NMR (acetone-d_6): 170.6; 162.6; 160.6; 158.7; 155.9; 137.3; 129.3; 128.9; 128.8; 127.3; 96.1; 79.9; 74.4; 66.9; 46.5; 38.2; 28.6; 12.6. MALDI-FTMS $[M+Na]^+$: calculated: 557.0620; observed: 557.0634.

4.2.5. Synthesis of oxazole building block 11b. As described for **11a**. Purification of **11b** was accomplished on silica gel with EtOAc/hexanes=1:5. Yield: 65%. ^{1}H NMR (acetone-d_6): 7.34–7.24 (m, 5H); 6.49 (d, J=8.3 Hz, 1H); 5.05 (m, 1H); 4.56 (m, 2H); 3.87 (m, 2H); 3.82 (s, 3H); 2.57 (s, 3H); 1.42 (s, 9H). ^{13}C NMR (acetone-d_6): 163.2; 161.4; 157.2; 156.1; 139.3; 129.1; 128.5; 128.4; 128.3; 79.7; 73.5; 71.1; 51.8; 49.9; 28.6; 12.1. MALDI-FTMS $[M+Na]^+$: calculated: 413.1683; observed: 413.1681.

4.2.6. Synthesis of thiazole building block 11c. As described above. Amidoketone compound **10a** was dissolved in anhydrous THF (0.1 M) and Lawesson's reagent (1.5 equiv.) was added. The mixture was stirred under reflux for 5 h. The solvent was removed and the residue was dissolved in EtOAc, extracted with water, 5% HCl

solution, saturated $NaHCO_3$ solution and brine, then dried over $MgSO_4$ and concentrated in vacuo. Thiazole containing building block **11c** was purified by chromatography on silica gel with EtOAc/hexanes=1:5. Yield: 54%. ^{1}H NMR (acetone-d_6): 7.37–7.34 (m, 5H); 6.91 (d, J=8.3 Hz, 1H, NH); 5.35 (m, 1H); 5.15 (m, 2H); 5.09 (m, 2H); 3.25 (dd, ^2J=16.2 Hz, ^3J=6.1 Hz, 1H); 3.08 (dd, ^2J=16.2 Hz, ^3J=7.4 Hz, 1H); 2.78 (s, 3H); 1.43 (s, 9H). ^{13}C NMR (acetone-d_6): 170.9; 169.8; 160.9; 156.0; 147.8; 140.6; 137.3; 129.3; 128.9; 96.3; 80.1; 74.7; 67.0; 50.6; 39.0; 28.6; 13.6. MALDI-FTMS $[M+Na]^+$: calculated: 573.0391; observed: 573.0364.

4.2.7. Synthesis of thiazole building block 11d. As described for **11c**, with purification on silica gel with EtOAc/hexanes=1:4. Yield: 65%. ^{1}H NMR (acetone-d_6): 7.36–7.24 (m, 5H); 6.72 (d, 1H); 5.11 (m, 1H); 4.58 (m, 2H); 3.91 (m, 2H); 3.83 (s, 3H); 2.71 (s, 3H); 1.43 (s, 9H). ^{13}C NMR (acetone-d_6): 168.3; 163.5; 156.3; 145.5; 141.9; 139.3; 129.1; 128.5; 128.4; 79.8; 73.6; 72.2; 54.1; 51.9; 28.6; 13.1. MALDI-FTMS $[M+Na]^+$: calculated: 429.1460; observed: 429.1449.

4.2.8. Synthesis of trioxazole triacid platform 5a. (1) *The one-pot procedure*. Module **11a** was successively subjected to trichloroethyl and Boc deprotection (Section 4.2) to give amino acid compound **13a**. To the stirred solution of this module at 0.05 M in anhydrous DMF was added DIEA (1 equiv.) and PyBOP (2 equiv.), followed by the slow addition of DIEA (9 equiv.) at rt. The mixture was stirred for 14 days, and was worked-up as described for general peptide coupling. Purification was accomplished on silica gel using EtOAc/hexanes=2:3. The isolated benzyl-protected **14a** was further purified by crystallization from EtOAc upon addition of hexanes to form a white powder in 38% yield. Cyclotetramer compound **15a** was also separated by column chromatography in 24% as a yellow oil. Protected platform **14a** was dissolved in EtOAc (0.01 M), Pd–C (10%) (0.1 g/mmol starting material) was added, and the mixture was stirred for 20 h at rt under H_2. The mixture was filtered through Celite®521 (Aldrich), and concentrated in vacuo to give pure trioxazole triacid platform **5a** quantitatively. (2) *The stepwise procedure*. The oxazole building block **11a** was first subjected to Boc deprotection (see Section 4.2) to give the TFA salt of amino compound **16a**. Peptide coupling with acid monomer **12a** was carried out as usual (see Section 4.2). Pure protected oxazole dimer **17a** was isolated in 64% after column chromatography on silica gel with EtOAc/hexanes=1:2. Boc deprotection, coupling with acid monomer **12a** and purification were repeated to give protected trimer compound **18a** again in 64% yield. After trichloroethyl and Boc deprotections of compound **18a** (see Section 4.2) the residue was dissolved in anhydrous DMF (0.005 M), PyBOP (2 equiv.) and DIEA (10 equiv.) were added at rt and the mixture was stirred for 4 days. Work-up and purification procedures were the same as in the case of the one-pot reaction. Pure, protected cyclotrimer platform **14a** was isolated in 69%. Deprotection of benzyl esters was carried out as described above to yield pure triacid platform **5a**. ^{1}H NMR (acetone-d_6): 8.45 (d, J=5.1 Hz, 3H, NH); 5.33 (m, 3H); 3.19 (dd, ^2J=16.1 Hz, ^3J=5.9 Hz, 3H); 3.16 (dd, ^2J=16.1 Hz, ^3J=4.3 Hz, 3H); 2.61 (s, 9H). ^{13}C NMR (acetone-d_6): 171.0; 161.4; 161.2; 154.8; 129.28; 46.6; 38.0; 11.6. MALDI-FTMS $[M+Na]^+$: calculated: 611.1344; observed: 611.1338.

4.2.9. Synthesis of trioxazole trialcohol platform 5b. (1) *The one-pot procedure*. Module **11b** was successively subjected to methyl and Boc deprotection (see Section 4.2) to give amino acid compound **13b**. To the stirred solution of this module at 0.02 M in anhydrous DMF (0.02 M) was added DIEA (1 equiv.), DPPA (3 equiv.) followed by the slow addition of DIEA (7.5 equiv.) at 0°C. The mixture was stirred for 4 days slowly warmed to rt. It was worked-up as in the case of general peptide couplings. Purification was accomplished on silica gel using EtOAc/hexanes=1:1 to give **14b** in 35%. Platform **14b** was dissolved in a mixture of EtOH/EtOAc=1:1 (0.01 M) and palladium hydroxide (0.45 g/mmol starting material) was added. The mixture was stirred under an H_2 atmosphere for 2 days, filtered through celite and concentrated in vacuo to give the pure triol **5b** in 90% yield. (2) *The stepwise procedure*. Oxazole **11b** was first subjected to Boc deprotection (see Section 4.2) to give the TFA salt of amino compound **16b**. Peptide coupling of **16b** (1 equiv.) with acid monomer **12b** (1 equiv.) was carried out using PyBOP (1.2 equiv.) activation in the presence of DIEA (3.8 equiv.) in anhydrous DMF (0.06 M) at rt for 24 h. Work-up as for general peptide coupling. Pure protected oxazole dimer **17b** was isolated in 72% yield after column chromatography on silica gel with EtOAc/hexanes=1:2. Boc deprotection and coupling with acid monomer **12b** were repeated to give protected trimer compound **18b** (89%). After methyl and Boc deprotections (see Section 4.2) the residue was dissolved in anhydrous DMF (0.01 M), PyBOP (2.2 equiv.) and DIEA (7.6 equiv.) were added at rt and the mixture was stirred for 4 days. Work-up and purification was the same as in the one-pot reaction. Symmetric, protected cyclotrimer platforms (**14b** and its enantiomer) were isolated in 15% yield; diastereomeric asymmetric platforms (**19** and its enantiomer) were isolated in 26%. Deprotection of benzyl esters on platform **14b** was carried out as described above to yield platform **5b**. ^{1}H NMR (DMSO-d_6): 8.34 (d, J=6.1 Hz, 3H); 5.20 (t, J=5.9 Hz, 3H); 5.07 (m, 3H); 3.93 (m, 3H); 3.86 (m, 3H); 2.61 (s, 9H). ^{13}C NMR (DMSO-d_6): 159.7; 159.6; 153.4; 127.9; 61.4; 50.6; 11.3. MALDI-FTMS $[M+Na]^+$: calculated: 527.1497; observed: 527.1473.

4.2.10. Synthesis of trithiazole triacid platform 5c. The applied one-pot procedure using module **11c** was the same as in the case of building block **11a** and gave protected cyclotrimer **14c** in 36% and cyclotetramer **15c** in 16%. For Bzl-ester deprotection, compound **14c** was dissolved in anhydrous $CHCl_3$ (0.01 M) and $(CH_3)_3SiI$ (20 equiv.) was added at 40°C. The mixture was stirred for 20 h then quenched with water. The organic solvent was removed in vacuo and the residue was diluted with 10% $NaHSO_3$ solution. This mixture was extracted with EtOAc several times and the combined organic layers were washed with saturated $NaHCO_3$ solution. The basic aqueous phase was acidified with 5% $KHSO_4$ solution to pH~3–4 and re-extracted with EtOAc. The organic layer was washed with brine then concentrated in vacuo to give pure trithiazole **5c**. ^{1}H NMR (acetone-d_6): 8.77 (d, J=8.6 Hz, 3H, NH); 5.84 (m, 3H); 3.10 (dd, ^2J=16.4 Hz, ^3J=4.8 Hz, 3H); 2.95 (dd, ^2J=16.4 Hz, ^3J=8.7 Hz, 3H); 2.79 (s, 9H). ^{13}C NMR

(acetone-d_6): 171.7; 165.1; 161.7; 142.7; 48.0; 42.1; 12.6. MALDI-FTMS $[M+Na]^+$: calculated: 637.084; observed: 637.0833.

4.2.11. Synthesis of trithiazole trialcohol platform 5d. The one-pot procedure was applied on module **11d** as in the case of **11b**. The pure protected cyclotrimer **14d** was obtained in 22% yield. (The diastereomeric platform with *syn–syn–anti* side-chain configuration was also separated in 7% yield.) For Bzl-ester deprotection, compound **14d** was dissolved in anhydrous $CHCl_3$ (0.01 M) and $(CH_3)_3SiI$ (20 equiv.) was added at 40°C. The mixture was stirred for 30 h then quenched with water. The organic solvent was removed in vacuo and the residue was diluted with 10% $NaHSO_3$ solution. This mixture was extracted with EtOAc several times and the combined organic layers were washed with saturated $NaHCO_3$ solution, brine and concentrated in vacuo to give pure trithiazole trialcohol platform **5d** in quantitative yield. ^{1}H NMR ($CDCl_3$/acetone-d_6=2:1): 8.60 (d, J=8.0 Hz, 3H, NH); 5.44 (m, 3H); 3.96 (dd, ^2J=10.7 Hz, ^3J=4.8 Hz, 3H); 3.77 (dd, ^2J=10.7 Hz, ^3J=6.9 Hz, 3H); 2.79 (s, 9H). ^{13}C NMR ($CDCl_3$/acetone-d_6=2:1): 163.2; 161.7; 142.2; 141.9; 65.7; 52.9; 12.7. MALDI-FTMS $[M+Na]^+$: calculated: 575.0812; observed: 575.0797.

4.3. Synthesis of acetol- (20a) and *tert*-butyl (20b) protected modules

Compound **11a** was subjected to Bzl ester deprotection under hydrogenolytic conditions (as in the one-pot synthesis of **5a**). The residue (1 equiv.) was dissolved in anhydrous THF (0.02 M) and TBC (1.2 equiv.) was added, followed by the slow addition of TEA (1.2 equiv.) at rt. The mixture was stirred for 20 min, filtered and the solvent was removed in vacuo to give the active ester. To the stirred solution of acetol (2 equiv.) or ^{t}Bu–OH (2 equiv.) and DMAP (2 equiv.) in anhydrous DCM (0.02 M) was added the DCM solution of the active ester compound at 0°C. The mixture was stirred for 2 h and was allowed to warm to rt, then concentrated in vacuo and purified on silica gel using EtOAc/hexanes=1:2. Yield of acetol-ester (**20a**) and *tert*-butyl ester (**20b**) were 83 and 52%, respectively.

20a. ^{1}H NMR (acetone-d_6): 6.70 (d, J=8.6 Hz, 1H, NH); 5.26 (m, 1H); 5.08 (s, 2H); 4.73 (s, 2H); 3.22 (dd, ^2J=16.6 Hz, ^3J=6.6 Hz, 1H); 3.10 (dd, ^2J=16.6 Hz, ^3J=6.9 Hz, 1H); 2.68 (s, 3H); 2.13 (s, 3H); 1.42 (s, 9H). ^{13}C NMR (acetone-d_6): 202.0; 170.3; 162.6; 160.7; 158.9; 155.9; 127.3; 96.2; 79.9; 74.4; 69.4; 46.4; 37.8; 28.6; 26.1; 12.6. MALDI-FTMS $[M+Na]^+$: calculated: 523.0412; observed: 523.0424.

20b. ^{1}H NMR (acetone-d_6): 6.63 (d, J=8.7 Hz, 1H, NH); 5.21 (m, 1H); 5.07 (m, 2H); 2.98 (dd, ^2J=15.8 Hz, ^3J=7.0 Hz, 1H); 2.83 (dd, ^2J=15.8 Hz, ^3J=7.8 Hz, 1H); 2.67 (s, 3H); 1.42 (s, 18H). ^{13}C NMR (acetone-d_6): 169.9; 162.8; 160.8; 158.8; 155.9; 127.2; 96.2; 81.4; 79.8; 74.4; 46.7; 39.6; 28.6; 28.2; 12.6. ESI-MS $[M+Na]^+$: calculated: 523.0; observed: 523.0.

4.3.1. Synthesis of orthogonally protected platform 23. Modules **20a** and **20b** were subjected to trichloroethyl ester cleavage (see Section 4.2) to give acids **21a** and **21b**, respectively. These were coupled to amino compound **16a** in a stepwise fashion as in the synthesis of platform **5a**. The amounts of reagents used were the following: **21a** (1 equiv.), **16a** (1.2 equiv.), HBTU (2 equiv.), HOBt (2 equiv.), DIEA (6 equiv.) in anhydrous DMF (0.1 M) for 4 days. The work-up procedure was the same as for general peptide coupling reactions. Purification was accomplished on silica gel with EtOAc/hexanes=1:2 to give the protected dimer in 68%. After Boc deprotection of the dimer compound (1 equiv.) (see Section 4.2) acid building block **21b** was coupled using the same procedure as previously. Completely protected linear trimer **22** was isolated in 32% yield after column chromatography on silica gel with EtOAc/hexanes=1:1. The trichloroethyl ester group was removed using the general procedure, whereas the following Boc cleavage was carried out in DCM (0.03 M) using only 20 equiv. of TFA for 1 h at rt. The solvent was evaporated and the residue was dissolved in anhydrous DMF (0.01 M), PyBOP (2 equiv.) and DIEA (10 equiv.) were added at rt and the mixture was stirred for 10 days. The work-up was the same as in the general case for peptide couplings and purification was accomplished on a preparative chromatographic plate using EtOAc/hexanes=2:1. Pure orthogonally protected platform **23** was isolated in 24% (from linear trimer **22**). ^{1}H NMR (acetone-d_6): 8.51 (d, J=5.3 Hz, 1H, NH); 8.47 (d, J=5.3 Hz, 1H, NH); 8.45 (d, J=5.6 Hz, 1H, NH); 7.36–7.30 (m, 5H); 5.38 (m, 2H); 5.33 (m, 1H); 5.10 (AB, J=12.3 Hz, 1H); 5.06 (AB, J=12.3 Hz, 1H); 4.71 (s, 2H); 3.27 (m, 2H); 3.20 (m, 2H); 3.08 (dd, ^2J=15.3 Hz, ^3J=4.0 Hz, 1H); 2.98 (dd, ^2J=15.3 Hz, ^3J=6.6 Hz, 1H); 2.63 (s, 3H); 2.61 (s, 3H); 2.53 (s, 3H); 2.09 (s, 3H); 1.37 (s, 9H). ^{13}C NMR (acetone-d_6): 201.5; 169.8; 169.5; 169.1; 161.4; 161.3; 161.2; 161.1; 160.8; 160.8; 155.0; 154.9; 154.8; 137.0; 129.4; 129.3; 129.2; 129.2; 129.0; 81.7; 69.4; 67.1; 46.7; 46.6; 46.4; 40.2; 38.9; 38.2; 28.2; 26.0; 11.6; 11.5. MALDI-FTMS $[M+Na]^+$: calculated: 813.2702; observed: 813.2719.

4.3.2. Synthesis of monoacid platform 24 and diacid platform 25. To the stirred solution of orthogonally protected platform **23** (1 equiv.) in anhydrous THF (0.01 M) was added TBAF (8 equiv., as a 1 M solution in THF) at rt and stirring was continued for 4 h. The mixture was diluted with water (to 1.5 times the original volume) and concentrated in vacuo. The residue was dissolved in EtOAc, extracted with 5% aqueous $KHSO_4$ solution and brine, and dried over Na_2SO_4. The residue contained monoacid platform **24** in 80%. ^{1}H NMR (acetone-d_6): 8.51 (d, J=5.3 Hz, 1H, NH); 8.48 (d, J=5.4 Hz, 1H, NH); 8.47 (d, J=5.7 Hz, 1H, NH); 7.36–7.32 (m, 5H); 5.40–5.34 (m, 3H); 5.10 (AB, J=12.3 Hz, 1H); 5.07 (AB, J=12.3 Hz, 1H); 3.21 (m, 2H); 3.18 (m, 2H); 3.08 (dd, ^2J=15.3 Hz, ^3J=4.2 Hz, 1H); 3.00 (dd, ^2J=15.3 Hz, ^3J=6.4 Hz, 1H); 2.64 (s, 3H); 2.61 (s, 3H); 2.54 (s, 3H); 1.38 (s, 9H). ^{13}C NMR (acetone-d_6): 170.9; 169.8; 169.0; 161.5; 161.3; 161.2; 161.1; 160.9; 155.9; 154.8; 137.0; 129.4; 129.3; 129.2; 129.2; 129.0; 81.7; 67.1; 46.7; 46.6; 46.5; 40.2; 38.9; 38.1; 28.2; 11.6; 11.5. MALDI-FTMS $[M+Na]^+$: calcd: 757.244; observed: 757.2445.

Monoacid platform **24** was subjected to ^{t}Bu ester deprotection using general Boc cleavage conditions to give a

quantitative yield of diacid **25**. ^{1}H NMR (acetone-d_6): 8.48 (m, 3H, NH); 7.36–7.30 (m, 5H); 5.40–5.35 (m, 3H); 5.08 (m, 2H); 3.22 (m, 3H); 3.19 (m, 3H); 2.63 (s, 3H); 2.61 (s, 3H); 2.53 (s, 3H). ^{13}C NMR (acetone-d_6): 171.0; 169.9; 161.5; 161.4; 161.4; 161.3; 161.2; 160.9; 154.9; 154.9; 154.8; 137.0; 129.4; 129.3; 129.3; 129.2; 129.2; 129.1; 67.2; 46.7; 46.6; 46.5; 38.9; 38.2; 38.1; 11.6; 11.5. MALDI-FTMS $[M+Na]^+$: calculated: 701.1814; observed: 701.1830.

Acknowledgements

Financial support from the Skaggs Foundation and the National Institutes of Health is acknowledged with gratitude. Gebhard Haberhauer thanks the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship. The authors also express their special thanks to Professors Takeharu Haino of Hiroshima University and Peter Wipf of the University of Pittsburgh for advice and encouragement.

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18. The methyl ester deprotection of compound 18b resulted in partial epimerization of its chiral centers. This lead to a mixture of diastereomers which were not separated but subjected to Boc cleavage and cyclization. Two cyclic compounds were isolated after silica gel chromatography: a symmetric and an asymmetric one, along with their enantiomers. If there is equal probability for all three chiral centers to epimerize, the theoretical ratio between the four possible diastereomers (*syn–syn–syn*: *syn–syn–anti*: *syn–anti–anti*: *anti–anti–anti*) is 8:12:6:1. This has been found experimentally by coupling the symmetrical and asymmetrical triol platforms with Boc-(L)-Asp(OBzl)-OH. In both cases two diastereomers were separated in the ratio calculated above.
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